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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/075,322 | 02/14/2002 | David T. Curiel | D6392 | 8688 |

7590 05/04/2007

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| EXAMINER | |
|---|---|
| NGUYEN, QUANG | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 05/04/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/075,322 | CURIEL ET AL. | |
| | Examiner | Art Unit | |
| | Quang Nguyen, Ph.D. | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4-7 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's amendment filed on 2/23/07 was entered.

Claims 1, 4-7 and 10-12 are pending in the present application, and they are examined on the merits herein.

### *Response to Amendment*

The rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement was withdrawn in light of the Declaration of Deposit filed on 2/23/07.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al. (WO 98/40508; Cited previously) in view of Muzykantov et al. (Am. J. Physiol. 270: L704-L713, 1996; IDS) for the same reasons already set forth in the Office Action mailed on 10/26/05 (pages 4-7). ***The same rejection is restated below.***

Sosnowski et al. disclose a re-targeted, tropism-modified adenoviral vector system that specifically target cells expressing a preselected receptor, comprising an antibody or fragment thereof that binds an adenoviral capsid protein (including an adenoviral knob protein); a targeting ligand that binds the preselected receptor; and an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter (including a tissue-specific promoter); wherein the ligand is conjugated to the antibody or fragment thereof and wherein the antibody or fragment thereof is bound to the adenovirus (page 4, lines 17-25; page 8, line 27 continues to line 1 of page 9). Sosnowski et al further teach that tissue specific promoters are particularly useful for expression in a wide variety of cells, including endothelial and smooth muscle cells, and by using one of this class of promoters, an extra margin of specificity can be attained (page 75, lines 3-5). Exemplary endothelial-specific promoters include VEGF-receptor promoter among others (page 75, line 17 continues to line 19 of page 76). Sosnowski et al. further teach the utilization of bi-specific antibodies (see the section on Bi-specific Antibodies, pages 28-33, particularly page 30,

lines 14-17) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. Sosnowski et al. also teach that any antibody that recognizes a molecule internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others (see pages 43-48).

Sosnowski et al. do not teach specifically the utilization of a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, more specifically a bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody, in their tropism-modified adenoviral vector system.

However, at the effective filing date of the present application Muzykantov et al. already disclose that the Mab 9B9 to angiotensin converting enzyme is a safe, specific and useful carrier for drugs targeting to the pulmonary vascular endothelium after systemic administration, and that Mab 9B9 is internalized by endothelial cells both *in vitro* and *in vivo* without significant intracellular degradation (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the retargeted, tropism-modified adenoviral vector system of Sosnowski et al. by utilizing a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, and more specifically the bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody to target the modified

adenoviral vector containing a transgene specifically to pulmonary vascular endothelium after a systemic delivery in light of the teachings of Muzykantov.

An ordinary skilled artisan would have been motivated to carry out the above modification because Muzykantov et al. already teach that Mab 9B9 **is a safe, specific and useful carrier for drugs targeting specifically to the pulmonary vascular endothelium after systemic administration** and that the antibody is internalized by endothelial cells both *in vitro* and *in vivo* and that it is not significantly degraded intracellularly. Moreover, Sosnowski et al. clearly teach that **any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells, and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob**. The modified re-targeted, tropism-modified adenoviral vector system would result in increasing targeting specificity to pulmonary vascular endothelial cells expressing angiotensin converting enzyme and reducing transgene expression in non-pulmonary vascular endothelial cells.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Sosnowski et al. and Muzykantov et al., coupled with a high level of skills of an ordinary skilled artisan in the art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

***Response to Arguments***

Applicants' arguments related in part to the above rejection in the Amendment filed on 2/23/07 (pages 8-10) have been fully considered, but they are not found persuasive.

It is noted that Applicants reiterated the same lines of arguments and these have been adequately addressed by the Examiner in the previous Office Action mailed on 8/18/06 (pages 9-11).

With respect to the issue that the bi-specific antibody allegedly taught by Sosnowski et al is conjugated to anti-Ad5 knob protein on one end and to a polypeptide targeting a cell surface receptor on the other, it should be noted that polypeptides reactive with an FGF receptor are exemplary targeting ligands (page 28, lines 23-27). Moreover, Sosnowski et al teach clearly that **any antibody that recognizes a molecule internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others can be used as ligands** (see pages 43-48).

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds et al. (Mol. Ther. 2: 562-578, 2000) in view of Sosnowski et

al. (WO 98/40508; Cited previously) for the same reasons already set forth in the Office Action mailed on 10/26/05 (pages 10-12). ***The same rejection is restated below.***

Reynolds et al disclose a targetable, injectable adenoviral vector for selective gene delivery to pulmonary endothelium *in vivo*, said vector comprises a bispecific antibody (Mab 9B9 conjugated to 1D6.14 anti-knob Fab antibody) that target Ad infection specifically to angiotensin-converting enzyme, which is preferentially expressed on pulmonary capillary endothelium (see abstract and the Methods section). Reynolds et al further teach that administration of retargeted vector complex via tail vein injection into rats resulted in at least a 20-fold increase in both Ad DNA localization and luciferase transgene expression in the lungs, compared to the untargeted vector. Additionally, targeting led to reduced transgene expression in nontarget organs, especially the liver, where the reduction was over 80%. Reynolds et al. also state that "However, further refinements to avoid nonspecific uptake of vector by the reticuloendothelial system may be required for optimal efficacy" (page 577, col. 1, bottom of second paragraph).

Reynolds et al do not specifically teach the use of any tissue specific promoter, including the vascular endothelial growth factor type I receptor promoter, in the disclosed adenoviral vector for expressing a transgene.

However, at the effective filing date of the present application Sosnowski et al. already disclose a re-targeted, tropism-modified adenoviral vector system that specifically target cells expressing a preselected receptor, comprising an antibody or fragment thereof that binds an adenoviral capsid protein (including an adenoviral knob

protein); a targeting ligand that binds the preselected receptor; and an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter (including a tissue-specific promoter); wherein the ligand is conjugated to the antibody or fragment thereof and wherein the antibody or fragment thereof is bound to the adenovirus (page 4, lines 17-25; page 8, line 27 continues to line 1 of page 9). Sosnowski et al teach specifically that tissue specific promoters are particularly useful for expression in a wide variety of cells, including endothelial and smooth muscle cells, and by using one of this class of promoters, an extra margin of specificity can be attained (page 75, lines 3-5). Exemplary endothelial-specific promoters include VEGF-receptor promoter among others (page 75, line 17 continues to line 19 of page 76).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the targetable, injectable adenoviral vector system of Reynolds et al. by also incorporating the use of an endothelial cell specific promoter such as VEGF-receptor promoter in light of the teachings of Sosnowski et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Sosnowski et al already teach **the use of an endothelial cell specific promoter provides an extra margin of specificity** (page 75, lines 3-5), and that this would be a refinement that avoids the nonspecific uptake and non-specific expression of a transgene in non-targeted cells *in vivo*.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Reynolds et al. and

Sosnowski et al., coupled with a high level of skills of an ordinary skilled artisan in the art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

***Response to Arguments***

Applicants' arguments related in part to the above rejection in the Amendment filed on 2/23/07 (page 12) have been fully considered, but they are not found persuasive.

It is noted that Applicants reiterated the same lines of arguments and these have been adequately addressed by the Examiner in the previous Office Action mailed on 8/18/06 (pages 14-15).

Once again, the examiner has provided the teachings of Reynolds et al., Sosnowski et al., motivation for the combination of these references, particularly Sosnowski et al already teach **the use of an endothelial cell specific promoter provides an extra margin of specificity** (page 75, lines 3-5), and that this would be a refinement that avoids the nonspecific uptake and non-specific expression of a transgene in non-targeted cells *in vivo*, as well as a reasonable expectation of success; and therefore the examiner has established that the claimed invention as a whole was *prima facie* obvious. This is not the situation of trying as alleged by Applicants.

## *Conclusion*

***No claims are allowed.***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

**To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.**

**Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.**

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QUANG NGUYEN, PH.D.
PRIMARY EXAMINER